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ORIGINAL ARTICLE

The long-term surgical outcomes of low-grade epilepsy-associated neuroepithelial tumors

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Abstract

Objective: This study aimed to evaluate the surgical outcomes and relevant prognostic factors in patients with low-grade epilepsy-associated neuroepithelial tumors (LEAT) and, especially, to develop a scoring system to predict postoperative seizure outcomes.

Methods: The clinical data of patients who underwent epilepsy surgery for LEAT were retrospectively studied. The surgical outcomes of seizure and neurological statuses in patients were evaluated using Engel classification and modified Rankin Scale (mRS) scoring, respectively. A scoring system of seizure outcomes was constructed based on the weight of the β-coefficient estimate of each predictor in the final multivariate predicting model of seizure outcomes.

Results: Of the 287 patients (106 female) enrolled, the median age was 19 years at surgery and 10 years at seizure onset, with a median duration of epilepsy of 60 months. Among 258 patients who were followed up for at least 12 months, 215 (83.3%) patients had a favorable seizure outcome (Engel class I) after surgery, and 43 (16.7%) patients had an unfavorable seizure outcome; longer duration of epilepsy, discordant magnetoencephalography (MEG) findings, and acute postoperative seizures were significantly included in the scoring system to predict unfavorable seizure outcomes, and in the scoring system, accumulated scoring of 0–19 scores was recorded, which were finally grouped into three risk levels: low risk (risk < 30%), medium risk (30% ≤ risk < 70%), and high risk (risk ≥ 70%). In addition, favorable neurological outcomes (mRS score 0–1) were recorded in 187 (72.5%) patients, while unfavorable neurological outcomes were recorded in 71 (27.5%) patients, which were significantly related to poor seizure control, older age at surgery, and longer duration of epilepsy and hospitalization time.

Significance: The long-term surgical outcomes of LEAT after surgery were satisfactory. A scoring system for predicting unfavorable seizure outcomes with different risk levels was developed, which could partly guide clinical treatments of LEAT.

KEYWORDS
brain tumor, epilepsy surgery, neurological outcome, prognostic factor, seizure outcome

1 | INTRODUCTION

Brain tumors are the second most common epileptogenic etiologies in patients who undergo epilepsy surgery, second to focal cortical dysplasia (FCD) in children, and hippocampus sclerosis (HS) in adults.[1] Among them, low-grade epilepsy-associated neuroepithelial tumors (LEAT) are the most common tumor entities, reaching 80%–85%.[1,2] The term LEAT was first proposed by Luyken et al. for long-term epilepsy-associated tumors with clinical commonalities of slow tumor growth, long-term epilepsy history (often ≥2 years), predilection of temporal invasion, and seizure onset at young age (usually <18 years).[2,3] Recently, many tumor entities were included in the tumor spectrum of LEAT, including ganglioglioma (GG), dysembryoplastic neuroepithelial tumor (DNT), angiocentric glioma (AG), papillary glioneuronal tumor (PGNT), multinodular and vacuolating neuronal tumor (MVNT), pilocytic astrocytoma (PA), and some low-grade neuroepithelial tumors that were not otherwise specified (LGNET-NOS).[2–8]

In recent years, the surgical resection has been proved as an efficient treatment method for patients with epilepsy-related brain tumors, and patients with LEAT often have a favorable seizure outcome after epilepsy surgery, with seizure freedom reaching 75%–90%.[3,9–13] However, nearly 10%–30% of patients still suffer refractory seizures after operations, and associated risk factors, with an applicable predicting system of postoperative seizure outcomes, have not yet been well defined.[14–16] In addition, few studies concerned the long-term neurological outcome (or living status) in patients with LEAT after surgery,[16,17] which, however, is more important to evaluate patients with epilepsy who could finally return to normal life or work. Therefore, we retrospectively reviewed the surgical cases of LEAT in our single epilepsy center to further explore the postoperative seizure outcomes and relevant prognostic factors and to propose a scoring system for predicting seizure outcomes to guide clinical treatments. Also, postoperative neurological outcomes and related risk factors were studied in the study.

Key points

- The long-term surgical results of LEAT are satisfactory, with 83.3% of patients achieving seizure freedom and 72.5% of patients having favorable neurological status.
- A scoring system based on predictors of duration of epilepsy, concordance of MEG (or VEEG) findings, and acute postoperative seizures was developed to predict seizure outcomes for patients with LEAT.
- Unfavorable seizure outcomes, older age at surgery, longer epilepsy history, and hospital stay were found to predict unfavorable neurological outcomes.

2 | METHODS

2.1 | Patient selection

A retrospective chart review was conducted for all patients with epilepsy who underwent surgical treatment for LEAT between January 2008 and December 2020 at Sanbo Brain Hospital, Capital Medical University. This study was approved by the Capital Medical University Sanbo Brain Hospital Ethics Committee.

Patient selection criteria were as follows: (a) patients who had epilepsy caused by brain tumors that were histopathologically confirmed as low-grade glial or glioneuronal tumors based on the LEAT spectrum[2,4] were enrolled in the study; (b) patients who had a history of other invasive treatments or reoperation or without preoperative electrophysiological evaluations or complete clinical data were excluded. A total of 330 patients with the clinical diagnosis of LEAT were retrospectively reviewed, and however, 43 patients who did not meet the inclusion criteria were excluded. Finally, a total of 287 consecutive patients were included in the study; 258 (89.9%) patients were postoperatively followed up for at least 12 months, and their long-term seizure outcomes and neurological outcomes were analyzed (Figure S1).

2.2 | Preoperative examination and surgery

All patients underwent an individualized preoperative evaluation, including detailed medical history and physical examination, seizure semiology, electrophysiological monitoring of video electroencephalography (VEEG) or magnetoencephalography (MEG), and invasive stereotactic electroencephalogram (SEEG) as needed, and imaging examinations of brain magnetic resonance imaging (MRI) or positron emission tomography-computed tomography

(PET-CT) if necessary. In addition, neuropsychological evaluation was routinely recommended for patients before and after epilepsy surgery.

Brain MRI scans were performed in all patients. Lesion size was represented by the mean tumor diameter. Long-term VEEG monitoring was performed in all patients for at least 16 h, and the lateral concordant VEEG findings of interictal epileptiform discharges (IEDs) and ictal seizure rhythms were defined as epileptiform discharge sources localized in the same tumor-invading brain hemisphere. MEG measurements were routinely recommended to all patients with epilepsy, especially for those with discordant findings between lesion localization and seizure semiology or VEEG findings, which were performed in 146 (50.9%) patients with 120 min of continuous MEG data collection. Concordant MEG findings in each patient were defined as the interictal MEG spike sources confined to the perilesional brain areas or the same tumor-invading brain lobe. In addition, SEEG was performed in 16 (5.6%) patients who were with discordant findings between tumor location and seizure semiology or VEEG findings, or with tumors invading the eloquent brain area. Brain PET-CT measurements were performed in 49 (17.1%) patients.

After detailed preoperative evaluations by neurologists, neurosurgeons, neuroradiologists, and electrophysiologists, surgical plans were made. The aim of the operation was to remove the tumor and associated epileptogenic zone (EZ). The EZ was determined by the findings of the detailed preoperative evaluation and/or intraoperative electrocorticography (ECoG). Intraoperatively, neurological electrophysiological monitoring and neuronavigation were also performed for safe tumor resection. For patients whose EZ involved the eloquent brain area, bipolar electrocoagulation (similar to multiple subpial transections), with an output power of 4–5 Watts and a cortical interval of 5 mm, was used for the remaining epileptogenic area.[18] In particular, according to whether the intraoperative ECoG or SEEG was performed, surgical approaches were categorized as simple tumor resection (No) and tailored tumor resection (Yes).

2.3 | Follow-up examination

Patients were periodically followed up at the 3rd month and 6th month postoperatively and yearly thereafter. Follow-up evaluations of seizure outcomes and neurological outcomes were performed by neurosurgeons at the clinic and/or by telephone interview. Seizure outcomes were assessed according to the Engel classification,[19] and neurological outcomes were assessed by the modified Rankin Scale (mRS) scoring in each patient.[20] Favorable seizure outcomes were defined as Engel class I, and unfavorable seizure outcomes were Engel class II–IV at the last follow-up evaluation. Similarly, favorable neurological outcomes were defined as mRS scores of 0–1, while unfavorable neurological outcomes were defined as mRS scores of 2–6.

2.4 | Study variables and statistical analysis

Clinical variables of interest were evaluated for their correlations with seizure outcomes and neurological outcomes, including patient or demographic characteristics, lesion characteristics, seizure semiology, and electrophysiological findings, surgical and perioperative factors, and follow-up variables.

Continuous variables were described with medians and interquartile ranges (IQRs), while categorical variables were described with absolute and relative (%) frequencies. The outcome variable of seizure and neurological status was bicategorical as favorable (assigned as 0) and unfavorable (assigned as 1). Descriptive statistics between compared groups were analyzed by *t*-tests and χ^2 tests for continuous and categorical variables, respectively. When necessary, the Fisher's exact test and the Kruskal–Wallis rank-sum test were used. Variables showing a $P<0.05$ in the univariate analysis were then entered into the multivariate binary logistic regression model in a forward-LR fashion to test the association of combined predictors with the absolute outcomes of Engel classification and mRS scoring, respectively. Statistical tests were considered significant if $P<0.05$. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). All data were analyzed using the software package SPSS, version 20.

2.5 | LEAT scoring system for predicting seizure outcome

The β coefficient estimates from the final multivariate logistic regression model were used to develop a weighted point scoring system for clinical predictors for each patient with LEAT. Continuous variables were equally divided for the purpose of developing the point scoring system using clinical judgment. The points were added together across the predictor categories. According to the risk probability evaluation formula of $P=1/[1+\exp(-\text{logit})]$, we obtained the risk probability table of unfavorable seizure outcomes under the corresponding accumulated scores of clinical predictors.

3 | RESULTS

3.1 | Patient demographics

Among 287 patients, 106 (36.9%) patients were female, and 157 (54.7%) patients were adults. The median age at surgery was 19 years (IQR: 10.5–25 years), the median age at seizure onset was 10 years (IQR: 4–16 years), and the median duration of epilepsy was 60 months (IQR: 14–144 months; Table 1).

Upon admission, 222 (77.4%) patients had drug-resistant epilepsy. A total of 92 (32.1%) patients had at least one neurological deficit, including decreased memory, language, and/or intelligence to various degrees (84), various degrees of hemiparesis and/or hypermyotonia contralateral to the tumor (10), decreased vision (5), and hearing loss (1).

3.2 | Lesion characteristics

Of 287 tumors found by MRI, 139 (48.4%) cases were in the left brain, including two bilateral-invading tumors but prominently in the right brain. In particular, 184 (64.1%) patients had tumors located in the temporal lobe. Tumors located in the frontal, parietal, occipital, insular, and multiple lobes were found in 38 (13.2%), 19 (6.6%), 10 (3.5%), 3 (1.0%), and 33 (11.5%) cases, respectively. Among 33 multilobe invasive tumors, 21 cases extended to the temporal lobe as well, and thus, a total of 205 (71.4%) tumors had a temporal invasion. The median tumor size was 17.5 mm (IQR: 15–25 mm).

According to postoperative pathological records of surgical specimens, all 287 lesions were diagnosed as low-grade neuroepithelial tumors, including GG (209), DNT (41), AG (5), PA (1), PGNT (1), glioneuronal tumors (GNT) with mixed GG and DNT characteristics (mixed GNT, 17), and other LGNETs (13) (Table S1). Tumor-associated FCD was recorded in 70 patients (24.4%), including 34 (11.8%) cases of FCD II. In particular, the tumor marker $BRAF^{V600E}$ was detected by immunohistochemistry in 103 (35.9%) patients, of which 59 (57.3%) cases were $BRAF^{V600E}$ (+), including GG (51/84), DNT (5/13), and mixed GNT (3/6). In addition, 219 (76.3%) cases were tested with IDH mutations, but no IDH (+) was found in all tested lesions of GG (174), DNT (32), and other LGENTs (13).

3.3 | Seizure semiology and electrophysiological findings

Before surgery, 82 (28.6%) patients complained of daily seizure onset, while the other 205 (71.4%) patients experienced seizure onset weekly (105), monthly (63), quarterly (24), or yearly (13). A total of 191 (66.5%) patients had focal seizures (with or without awareness) as the most common seizure onset in recent years, but 96 (33.5%) patients had generalized seizures. In addition, history of seizure auras, bilateral or secondary generalized tonic–clonic seizures (GTCS), and status epilepticus

TABLE 1 Patient demographics, lesion characteristics, and follow-up evaluations based on tumor locations in 287 patients

Tumor location[a]	Temporal	Extratemporal	Multilobe	In total
Number of cases, n (%)	184 (64.1%)	70 (24.4%)	33 (11.5%)	287 (100%)
Female sex, n (%)	67 (36.4%)	23 (32.9%)	16 (48.5%)	106 (36.9%)
Age at surgery in years, median (IQR)	20 (11–26)	17 (9.5–22.3)	22 (10–27.5)	19 (10.5–25)
Adult patients (≥18 years), n (%)	107 (58.2%)	31 (44.3%)	19 (57.6%)	157 (54.7%)
Age at seizure onset in years, median (IQR)	11 (4–18)	9 (4.4–13.5)	8 (4–16)	10 (4–16)
Duration of epilepsy in months, median (IQR)	60 (18–120)	51 (12–168)	84 (15–150)	60 (14–144)
Drug-resistant epilepsy, n (%)	145 (78.8%)	52 (74.3%)	25 (75.8%)	222 (77.4%)
Left-side tumor, n (%)	92 (50%)	31 (44.3%)	16 (48.5%)	139 (48.4%)
Temporal-invading tumor, n (%)	184 (100%)	0 (0%)	21 (63.6%)	205 (71.4%)
Tumor-associated FCD, n (%)	53 (28.8%)	11 (15.7%)	6 (18.2%)	70 (24.4%)
Hospitalization time in days, median (IQR)	25 (19.3–30)	22.5 (18–30)	26 (17–35.5)	24 (19–30)
Follow-up time in months, median (IQR)	60 (33–84)	67 (48–88)	63 (48–87)	60 (38–84)
Seizure outcomes (Engel class I), n (%)[b]	138 (85.2%)	53 (81.5%)	24 (77.4%)	215 (83.3%)
Neurological outcomes (mRS score 0/1), n (%)[b]	121 (74.7%)	48 (73.8%)	18 (58.1%)	187 (72.5%)

Abbreviations: FCD, focal cortical dysplasia; IQR, interquartile range; mRS, modified Rankin scale.

[a]Tumors were grouped into three groups as temporal, extratemporal, and multilobe based on their prominent locations in the brain.

[b]The Engel classification and mRS scoring were evaluated in 258 patients who had postoperative follow-up for at least 12 months.

(SE) were recorded in 149 (51.9%), 175 (61.0%), and 11 (3.8%) patients, respectively.

Regarding VEEG findings, lateral concordant VEEG findings of IEDs were found in 193 (67.2%) patients, while discordant findings were found in 63 (22%) patients; 31 (10.8%) patients were unknown due to lack of significant IEDs or being in a normal EEG setting. Lateral concordant VEEG findings of ictal seizure rhythms were found in 135 (47%) patients, and discordant findings were found in 59 (20.6%) patients, but 93 (32.4%) patients were unknown due to no ictal seizures.

Among 146 (50.9%) patients with MEG examinations, the IEDs on MEG were recorded in 129 (88.4%) patients, while 17 (11.6%) patients had no significant epileptiform spikes. The concordant MEG findings were found in 81 (62.8%) patients, and discordant findings were found in 48 (37.2%) patients, while the other 158 patients were unknown.

3.4 | Surgical results

Intraoperative ECoG monitoring was performed in 231 (80.5%) patients. Complete tumor resection was achieved in 285 (99.3%) patients, except for two cases with subtotal tumor resection because of tumors invading brain eloquent areas. In total, tailored tumor resection was performed in 236 (82.2%) patients, and simple tumor resection was performed in 51 (17.8%) patients.

Postoperatively, 38 (13.2%) patients had acute seizures within the first 2 weeks after surgery. Operation-associated complications were met in 42 (14.6%) patients, including venous thrombosis (2), pulmonary infection (3), intracranial infection (11), hemorrhagic apoplexy (4), cerebral infarction (4), incision infection or poor healing (6), and others (14; such as electrolyte disorders, urinary tract infection, and gastrointestinal dysfunction). When discharged, a total of 112 (39.0%) patients had different degrees of neurological deficits, including decreased memory, language, and/or intelligence (93), decreased vision (11), various degrees of hemiparesis and hypermyotonia (24), mild facial paralysis (1), and eyelid drooping (3). The median hospitalization time was 24 days (IQR: 19–30 days).

3.5 | Follow-up outcomes

Among the 287 consecutive patients, 258 (89.9%) patients were postoperatively followed up for at least 12 months, while 29 (10.1%) patients were with follow-up time less than 12 months, including 11 (3.8%) patients with follow-up ranging from 3 to 12 months and 18 (6.3%) patients being lost because of no contact details. Of 258 patients who were followed up for at least 12 months, the median follow-up time was 60 months (IQR: 38–84 months). At the last follow-up evaluation, 215 (83.3%) patients were seizure-free and had a favorable seizure outcome (Engel Ia/187, Ib/5, Ic/20, and Id/3), while 43 (16.7%) patients still had seizure onset and thus had an unfavorable seizure outcome (Engel II/17, III/16, and IV/10; Figure S2). In total, 183 (70.9%) patients had anti-epileptic drugs (AEDs) reduced (61) or discontinued (122). During the whole period of follow-up (12–160 months), 9 (3.5%) patients had tumor recurrence (including one with subtotal tumor resection). Among them, 6/9 of cases had seizure recurrence, and 2 cases of GG (0.8%) had malignant progression.

Neurological outcomes were also evaluated in 258 patients at the last follow-up. Among them, 187 (72.5%) patients finally lived an independent life and could return to normal work or study, with a favorable neurological outcome (mRS 0/83, mRS 1/104; Figure S2). However, 71 (27.5%) patients could not return to normal life or needed extra help in life and thus had an unfavorable neurological outcome (mRS 2/59, mRS 3/5, mRS 4/2), including 5 cases of death (mRS 6) that was attributed to tumor malignant progression (2), seizure onset accident (1), and other diseases (2).

3.6 | Univariate and multivariate analyses of seizure outcomes

Univariate analysis found that clinical variables of patient age at surgery, duration of epilepsy, history of GTCS, drug-resistant epilepsy, lateral concordance of VEEG findings of IEDs or of ictal seizure rhythm, performance of MEG, concordance of MEG findings, acute postoperative seizures, and neurological outcomes were significantly different between the two groups of favorable and unfavorable seizure outcomes, with their P values < 0.05 (Table 2).

Multivariate binary logistic regression analysis found that the duration of epilepsy, concordance of MEG findings, and acute postoperative seizures were statistically correlated with seizure outcomes. In particular, patients who had a longer duration of epilepsy (OR = 1.01), discordant MEG findings (OR = 2.88), and acute postoperative seizures (OR = 3.67) were more likely to have an unfavorable seizure outcome (Table 3).

3.7 | Scoring system of seizure outcomes

Based on the significant variables by multivariate regression analysis above, a final logistic multivariate model was thus constructed as follows: Logit (seizure

TABLE 2 Univariate analyses of clinical variables between favorable and unfavorable seizure outcomes in 258 patients

Variable	Category	Favorable outcome	Unfavorable outcome	*P* value
Total, n (%)		215 (83.3%)	43 (16.7%)	
Gender, n (%)	Female	82 (82.8%)	17 (17.2%)	0.864
	Male	133 (83.6%)	26 (16.4%)	
Age at surgery in years, median (IQR)		18 (10–24)	24 (15–32)	0.001[a]
Age groups at surgery, n (%)	Pediatric (<18 years)	105 (88.2%)	14 (11.8%)	0.051
	Adult (≥18 years)	110 (79.1%)	29 (20.9%)	
Age at seizure onset in years, median (IQR)		11 (4–16.5)	9 (3.5–15)	0.290
Duration of epilepsy in months, median (IQR)		48 (12–108)	156 (72–240)	<0.001[a]
Drug-resistant epilepsy, n (%)	Yes	158 (79.8%)	40 (20.2%)	0.006[a]
	No	57 (95%)	3 (5%)	
Preoperative neurological deficits on admission, n (%)	Yes	69 (83.1%)	14 (16.9%)	0.952
	No	146 (83.4%)	29 (16.6%)	
Tumor side, n (%)	Right	112 (83.6%)	22 (16.4%)	0.911
	Left	103 (83.1%)	21 (16.9%)	
Tumor location, n (%)	Temporal	138 (85.2%)	24 (14.8%)	0.123
	Frontal	28 (80%)	7 (20%)	
	Parietal	17 (94.4%)	1 (5.6%)	
	Occipital	7 (77.8%)	2 (22.2%)	
	Insular	1 (33.3%)	2 (66.7%)	
	Multilobe	24 (77.4%)	7 (22.6%)	
Temporal invasion, n (%)	Yes	152 (84%)	29 (16%)	0.670
	No	63 (81.8%)	14 (18.2%)	
Tumor size in millimeter, median (IQR)		18.3 (13–26)	17.5 (15–25)	0.748
Tumor type, n (%)	GG	157 (84%)	30 (16%)	0.696
	DNT	33 (84.6%)	6 (15.4%)	
	Other LEAT	25 (78.1%)	7 (21.9%)	
Tumor calcification, n (%)	Yes	65 (86.7%)	10 (13.3%)	0.358
	No	150 (82%)	33 (18%)	
Tumor encystation, n (%)	Yes	34 (81%)	8 (19%)	0.651
	No	181 (83.8%)	35 (16.2%)	
Tumor-associated FCD, n (%)	Yes	52 (83.9%)	10 (16.1%)	0.896
	No	163 (83.2%)	33 (16.8%)	
Concomitant HS, n (%)	Yes	11 (73.3%)	4 (26.7%)	0.475
	No	204 (84%)	39 (16%)	
Main seizure type, n (%)[b]	Focal seizures	142 (83.5%)	28 (16.5%)	0.906
	Generalized seizures	73 (83%)	15 (17%)	
Seizure aura, n (%)	Yes	106 (80.9%)	25 (19.1%)	0.291
	No	109 (85.8%)	18 (14.2%)	
History of GTCS, n (%)	Yes	126 (79.2%)	33 (20.8%)	0.026[a]
	No	89 (89.9%)	10 (10.1%)	
History of SE, n (%)	Yes	10 (90.9%)	1 (9.1%)	0.783
	No	205 (83%)	42 (17%)	
Seizure frequency, n (%)	Daily	63 (80.8%)	15 (19.2%)	0.866
	Weekly	73 (83%)	15 (17%)	
	Monthly	49 (86%)	8 (14%)	
	Quarterly	19 (82.6%)	4 (17.4%)	
	Yearly	11 (91.7%)	1 (8.3%)	

TABLE 2 (Continued)

Variable	Category	Favorable outcome	Unfavorable outcome	*P* value
Lateral concordant VEEG findings of IEDs, n (%)	Yes	148 (86.5%)	23 (13.5%)	0.023[a]
	No	42 (71.2%)	17 (28.8%)	
	Unknown[c]	25 (89.3%)	3 (10.7%)	
Lateral concordant VEEG findings of ictal seizure rhythms, n (%)	Yes	105 (89.7%)	12 (10.3%)	0.001[a]
	No	38 (66.7%)	19 (33.3%)	
	Unknown[c]	72 (85.7%)	12 (14.3%)	
Performance of MEG, n (%)	Yes	104 (78.8%)	28 (21.2%)	0.045[a]
	No	111 (88.1%)	15 (11.9%)	
Concordant MEG findings, n (%)	Yes	59 (83.1%)	12 (16.9%)	0.001[a]
	No	30 (65.2%)	16 (34.8%)	
	Unknown[c]	126 (89.4%)	15 (10.6%)	
Performance of SEEG, n (%)	Yes	12 (75%)	4 (25%)	0.564
	No	203 (83.9%)	39 (16.1%)	
Performance of PET-CT, n (%)	Yes	36 (80%)	9 (20%)	0.509
	No	179 (84%)	34 (16%)	
Tailored tumor resection, n (%)	Yes	172 (82.3%)	37 (17.7%)	0.356
	No	43 (87.8%)	6 (12.2%)	
Perioperative complications, n (%)	Yes	31 (79.5%)	8 (20.5%)	0.484
	No	184 (84%)	35 (16%)	
Acute postoperative seizures within the first 2 weeks after surgery, n (%)	Yes	22 (59.5%)	15 (40.5%)	<0.001[a]
	No	193 (87.3%)	28 (12.7%)	
Hospitalization time in days, median (IQR)		24 (18–31)	24 (21–32)	0.315
Postoperative neurological deficits at discharge, n (%)	Yes	85 (84.2%)	16 (15.8%)	0.775
	No	130 (82.8%)	27 (17.2%)	
Follow-up time in months, median (IQR)		60 (37–84)	61 (42–97)	0.566
Tumor recurrence, n (%)	Yes	6 (66.7%)	3 (33.3%)	0.363
	No	209 (83.9%)	40 (16.1%)	
Neurological outcomes, n (%)	Favorable (mRS 0–1)	177 (94.7%)	10 (5.3%)	<0.001[a]
	Unfavorable (mRS 2–6)	38 (53.5%)	33 (46.5%)	

Abbreviations: DNT, dysembryoplastic neuroepithelial tumor; FCD, focal cortical dysplasia; GG, ganglioglioma; GTCS, generalized tonic–clonic seizure; HS, hippocampus sclerosis; IEDs, interictal epileptic discharges; IQR, interquartile range; LEAT, low-grade epilepsy-associated neuroepithelial tumors; MEG, magnetoencephalography; mRS, modified Rankin Scale; PET-CT, positron emission tomography-computed tomography; SEEG, stereotactic electroencephalography; SE, status epilepticus; VEEG, video electroencephalography.

[a]*P* <0.05, with significance.

[b]The main seizure type was defined as the most common type of seizure onset in the last year.

[c]Patients who had unknown results in lateral concordant VEEG findings of IEDs and of ictal seizure rhythms, and concordant MEG findings were recorded in 28 (no IEDs or normal VEEG findings), 84 (no ictus during VEEG monitoring), and 141 patients (no performance or no IEDs on MEG), respectively.

outcome) = β0 + β1 (duration of epilepsy, per month) + β2 (MEG findings, with discordant result) + β3 (MEG findings, with unknown result) + β4 (acute postoperative seizure) (Table 3).

In particular, a 36-month duration of epilepsy was assigned as one point, and thus, the scoring of the duration of epilepsy ranged from 0 to 10 points. According to the weight estimates, the scores of other predictors were obtained as follows: acute postoperative seizures (yes = 5 points, no = 0 points) and discordant MEG finding (yes = 4 points, no = 0 points, unknown = 2 points), with a total score of 0–19 points (Tables 3 and 4). According to the risk probability evaluation, we obtained the risk probability table under the corresponding score, which finally comprised three risk levels in predicting unfavorable seizure outcomes: low risk (0–6 points, risk <30%), medium risk (7–12 points, 30% ≤ risk < 70%), and high risk (13–19 points, risk ≥70%; Figure 1).

3.8 | Univariate and multivariate analyses of neurological outcomes

Univariate logistic regression analysis found that patient age at surgery, duration of epilepsy, drug-resistant epilepsy, lateral concordance of VEEG findings of ictal seizure rhythm, perioperative complications, hospitalization time, and seizure outcomes at the last follow-up evaluation were significantly related to postoperative neurological outcomes ($P < 0.05$; Table S2).

Multivariate binary logistic regression analysis found that patients' seizure outcomes (OR = 11.04), patient age at surgery (OR = 1.05), duration of epilepsy (OR = 1.01), and hospitalization time (OR = 1.06) were associated with patients' neurological outcomes (Table 5).

4 | DISCUSSION

Overall, the surgical results of LEAT are satisfactory, with 83.3% of patients achieving the long-term seizure freedom and 70.9% of patients with drug discontinued (47.3%) or reduced (23.6%), which is in line with the previous study.[9,13,14,16,21] In addition, the long-term neurological status of patients after surgery was also encouraging, with 72.5% of patients returning to normal work or study (mRS score 0–1).

TABLE 3 The related clinical predictors of the dependent variable of seizure outcomes in the multivariate logistic regression model[a]

	β	OR (95% CI)	*P* value
Duration of epilepsy, per month	0.008	1.01 (1.00–1.01)	<0.001
Concordance of MEG findings			0.019
(1) Discordant vs. concordant	1.058	2.88 (1.09–7.62)	0.033
(2) Unknown vs. concordant	−0.185	0.83 (0.34–2.04)	0.687
Acute postoperative seizures within the first 2 weeks after surgery	1.301	3.67 (1.56–8.65)	0.003

Abbreviations: CI, confidence interval; MEG, magnetoencephalography; OR, odds ratio.

[a]Patients with discordant MEG findings or with unknown results (no performance of MEG) were all compared to those with concordant MEG findings, and in particular, 15 patients with undetected IEDs on MEG were grouped into the unknown group. The receiver–operator characteristic curve (ROC) area was 0.83 (95% CI: 0.76–0.89).

TABLE 4 Proposed scoring scale of seizure outcomes in LEAT patients[a]

Predictor	Subgroup	Point[a]
Duration of epilepsy in years	<3	0
	3–6	1
	6–9	2
	9–12	3
	12–15	4
	15–18	5
	18–21	6
	21–24	7
	24–27	8
	27–30	9
	≥30	10
Concordance of MEG findings (or lateral concordance of VEEG findings of IEDs)	Concordant	0
	Discordant	4
	Unknown	2[b]
Acute postoperative epilepsy	No	0
	Yes	5

Abbreviations: IEDs, interictal epileptiform discharges; LEAT, low-grade epilepsy-associated neuroepithelial tumors; MEG, magnetoencephalography; VEEG, video electroencephalography.

[a]Detailed description of the predictors included in the proposed LEAT scoring system, with scoring value determined by weights of β coefficient estimates in the final multivariate regression model of seizure outcomes.

[b]Patients who were unknown with MEG (or VEEG) findings were assigned 2 points that were calculated by the mean value of the lowest point (0 points) and the highest point (4 points) to enroll those patients with no MEG evaluation (or normal VEEG findings) in the scoring system.

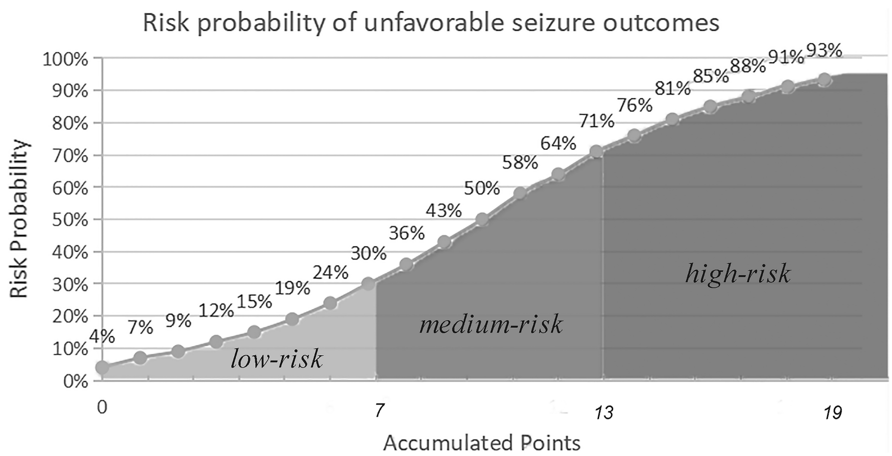

FIGURE 1 The risk probability of unfavorable seizure outcomes under accumulated points of clinical factors, with three risk levels: low risk: 0–6 points (risk <30%), medium risk: 7–12 points (risk: 30%–70%), and high risk: 13–19 points (risk ≥70%)

TABLE 5 Multivariate logistic regression analyses of clinical predictors of neurological outcomes

Variable	β	OR (95% CI)	*P* value
Age at surgery, per year	0.045	1.05 (1.01–1.08)	0.012
Duration of epilepsy, per month	0.006	1.01 (1.00–1.01)	0.004
Hospitalization time, per day	0.057	1.06 (1.02–1.10)	0.005
Unfavorable seizure outcome	2.402	11.04 (4.60–26.52)	<0.001

Note: The area under the receiver–operator characteristic (ROC) curve was 0.88 (95% CI: 0.84–0.93).
Abbreviations: CI, confidence interval; OR, odds ratio.

4.1 | Prognostic factors of seizure outcomes

Although most patients with LEAT have favorable seizure outcomes, approximately 10%–30% of patients still suffer poor seizure control or refractory seizures after epilepsy surgery.[14–16,21–25] Studies have found that some clinical factors significantly influence patients' seizure outcomes, but they have not yet been well defined or with inconsistent results in different LEAT (or GNT) surgical series.[9–16,21,24–31]

In the present study, possible clinical factors, including patient demographics, seizure semiology, and electrophysiological findings, tumor characteristics, surgical factors, and postoperative or follow-up results, were systematically evaluated, and we finally found the duration of epilepsy, concordance of MEG findings, and acute postoperative seizures were significantly correlated with postoperative seizure outcomes. The duration of epilepsy from seizure onset to surgery is commonly reported to predict postoperative seizure outcomes in patients with LEAT.[3,11,15,24] Previous studies have found that a long-term epilepsy history was associated with an unfavorable seizure outcome[3,14,24] and in our study. However, a few studies especially those with only pediatric cohorts reported no difference between the duration of epilepsy and seizure outcomes, while the age at surgery instead predicted seizure outcomes after surgery.[10,12,14] In our study, we included both pediatric and adult populations and did not find the correlation in age at surgery by multivariate analysis, even though a significant difference existed in the univariate analysis. The reason may lie in that for patients with LEAT, seizure onset usually begins at the ages of 10–15 years,[2,4] and the longer duration of epilepsy is thus accompanied by older ages in patients during surgery (by linear-regression analysis: $R^2 = 0.328$, $F = 125.1$, $P < 0.001$). Besides, the statistical significance of the correlations of the duration of epilepsy with seizure outcomes still existed in children ($P < 0.001$) and adults ($P < 0.001$) with further stratification analysis of the patient population. Therefore, we believe the duration of epilepsy, instead of the age at surgery, has a real influence on seizure outcomes.

With respect to electrophysiological factors, few studies have made an adequate or comprehensive analysis of their correlations with seizure outcomes due to the discordant or incomplete electrophysiological data (especially ictal VEEG and MEG findings) in their series.[10,12–14] Two previous studies have reported that patients with VEEG findings of local or unilateral epileptiform discharges had better seizure outcomes than those with bilateral or diffuse discharges,[3,32] which is in line with our results that patients who had lateral (or unilateral) concordant VEEG findings of either interictal or ictal discharge sources with tumor locations were more likely to have favorable seizure outcomes than those with discordant (or bilateral) discharges, but not in the multivariate model. In particular, we found that preoperative MEG findings had a better prediction for postoperative seizure outcomes than

VEEG findings in the multivariate predicting model, and patients with concordant MEG findings of IEDs often had favorable seizure outcomes. MEG is regarded as a useful diagnostic tool with the high spatiotemporal resolution for localizing interictal spikes for patients with epilepsy.[33,34] Despite the relatively low sensitivity (approximately 50%–70%) of MEG in localizing EZs, its specificity or accuracy is satisfying, reaching 80%–90%.[35–37]

In particular, clinical factors of seizure semiology and tumor characteristics were always found no correlations with seizure outcomes,[9–11,31,38–42] as well as in our study, although some studies reported that lack of GTCS onsets and temporal-invasive tumors predicted better seizure outcomes than others.[10,11,27] In our study, more than 70% of tumors were found with temporal invasion, which, however, did not influence the seizure outcomes when compared to those without temporal invasion. In addition, the surgical resection extent is found closely related to seizure outcomes in patients with LEAT.[3,10,11,15] In particular, postoperative remnant tumors are a significant risk factor for seizure outcomes.[14,15,27] However, complete tumor resection was achieved in most of our patients (nearly 99%), and thus, we could not observe the statistical difference.

For postoperative or follow-up factors, acute postoperative seizures were found to predict unfavorable seizure outcomes,[3,31] and we also found a correlation in our surgical cohort. The possible reason may be attributed to the incomplete resection of the EZ (seizures continue later) or the changed brain microenvironment at the surgical site (seizures discontinue later) during the early postoperative period. In particular, tumor recurrence or progression may cause seizure recurrence after surgery, although the frequency of tumor recurrence or progression is rather rare in LEAT patients.[2,3,27] In our cohort, tumor recurrence was found in nine patients during the long-term follow-up, of which six patients had seizure recurrence; however, seizure control was achieved in 4/5 of patients by reoperations.

4.2 | Scoring system of predicting seizure outcomes

Although many studies have reported the relevant risk factors for seizure outcomes in patients with LEAT after epilepsy surgery, there is no applicable scoring system for clinicians to predict patients' seizure outcomes.[14,15,23] Thus, we developed a scoring scale to predict LEAT seizure outcomes based on the significant clinical predictors of duration of epilepsy, concordance of MEG findings, and acute postoperative seizures with a total score of 0–19 points. Meanwhile, we divided the total scores into three risk levels according to the predicting risk of adverse results. In particular, patients who had unknown MEG findings due to no preoperative MEG examination or no detectable epileptiform discharges on MEG were assigned 2 points that were averaged by the concordant (0 points) and discordant (4 points) MEG findings to enroll those patients in the predicting system.

However, the predicting system may compromise for those LEAT cases with incomplete tumor resection, which was found to be a closely relevant risk factor for patients achieving final seizure control after surgery.[3,9–11] Even so, most patients, approximately 70%–100%, could finally achieve complete tumor resection and thus be a candidate enrolled in the predicting system.[3,9–11,21] In addition, detecting the epileptiform discharges in LEAT patients via the relatively expensive examination of MEG, instead of VEEG, may partly postpone the use of our predicting model, and thus, we further analyzed the multivariate predicting model by using the variable of lateral concordance of VEEG findings of IEDs to replace the MEG findings, which still significantly existed in the final predicting model (Table S3). Given this, we recommend to use the results of VEEG findings with the same scoring points if MEG data were absent (Table 4). For example, if a patient with GG had a 5-year epilepsy history before surgery (1 point), had no preoperative MEG examination but with discordant VEEG finding of IEDs (not 2 but 4 points), and suffered acute postoperative seizures (5 points), the total score obtained was 10 points, corresponding to the medium-risk group, with a risk of an unfavorable seizure outcome being predicted at 30%–70%. Further study with a large surgical cohort of LEAT from multiple centers is also needed to consolidate our scoring system or to develop a more applicable prediction model of seizure outcomes for patients with LEAT or low-grade brain tumors.

4.3 | Neurological outcome and predictors

The neurological outcomes (or living status) of patients with LEAT are seldom reported in previous studies, except that a few studies evaluated patients' psychosocial outcomes after surgery.[13,16,17] For example, Ehrstedt et al.[17] studied 28 cases of GNT with seizure onset in childhood and found a trend toward both higher educational level and employment status in adults who became seizure-free after surgery, and nearly 64% (9/14) of patients were employed full time in the seizure-free group compared with 0% in the epilepsy group.[17]

In this study, we evaluated the neurological outcomes of patients who were followed up at least 1 year after resection. Finally, we found that 72.5% of patients had a favorable outcome and could lead to a normal life after surgery (mRS score 0–1), while 27.5% of patients could not take part in previous work or study or needed extra life assistance (mRS scores ≥2), which may be attributed to adverse factors of poor seizure control, older age at surgery, longer epilepsy history, and hospitalization in our study. In particular, if patients had poor seizure control after surgery, it could significantly stop them from returning to normal life (OR = 11.04).[17,43,44] In particular, a shorter duration of epilepsy (or early surgical intervention) was also found to predict both favorable neurological outcomes and favorable seizure outcomes. It is worth noting that the psychological results in patients we believe may also influence patients' neurological outcomes;[9,16,41,45] however, the results were not studied in our study due to the missing data in most patients.

4.4 | Limitations

The evidence from our study with the LEAT cohort may compromise its retrospective nature, as well as its inhomogeneity, including several tumor types with different locations and age populations. However, the commonalities of these low-grade or developmental brain tumors with epilepsy are worthy of being discussed as one type of disease for clinical treatments; in addition, the comparison of the variables with different lesion locations and age populations could also tell us their real role-playing in surgical outcomes. Thus, our results might partly complement the undefined domains of the long-term surgical outcomes in patients with LEAT.

5 | CONCLUSIONS

Patients with LEAT could obtain satisfactory seizure control and neurological prognosis after epilepsy surgery. Based on the predictors of duration of epilepsy, concordance of MEG (or VEEG) findings, and acute postoperative seizures, a scoring system for predicting seizure outcomes was proposed to guide clinicians for LEAT treatments. In particular, early surgery for patients with LEAT is found to have both the benefits of achieving favorable seizure and neurological outcomes.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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